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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,379	08/02/2006	Tomas J. Ekstrom	2836-0163PUS1	8424

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EXAMINER	
EPPS -SMITH, JANET L	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
11/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/588,379	EKSTROM ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *2-11,13-20,32-61 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12,21-31,62,63 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-02-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 2-11, 13-20, 32-61 and 64 are withdrawn, and SEQ ID NO: 4-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4-27-2009.

2. Applicant's election with traverse of SEQ ID NO: 1-3 and 15-17, and Group 7, drawn to claims 21-25 and linking claims 1, 12, 26-31, 62-63, and 65-68, in the reply filed on 4-27-2009 is acknowledged. Moreover, in the reply filed 08/24/2009, Applicants further traversed this election. The traversal is on the ground(s) that at least claim 12, which links groups 5-7, is patentable and, accordingly, represents a contribution over the prior art. According to Applicants Chung et al. teaches a kinase, which is present in a cell *per se,* and is therefore distinguishable from the pharmaceutical composition of the instant claims. Contrary to Applicant's assertions, the technical feature linking all groups 1-11 is set forth in claim 1. This technical feature is drawn to pharmaceutical compositions comprising at least one compound capable of increasing gap-junction communication, and at least one nucleoside analogue, wherein said enhancing gap-junction communication is an aromatic acid, and further wherein the composition is used for the treatment of cancer in a patient. As stated in the two previous Office Actions, Chung et al. (2000) teaches a method for treating nasopharyngeal carcinoma comprising administering phenylbutyrate and ganciclovir, see abstract. Therefore, since groups 1-11 do not share a special technical feature that

makes a contribution over the prior art, the instant groups are considered to lack unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1, 12, 21-31, 62-63, and 65-68 are therefore pending for examination.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1 and 62, 65-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al. (1998; see IDS) or Chung et al. (2000). Claim 1 is drawn to a pharmaceutical compositions comprising at least one compound capable of increasing gap-junction communication, and at least one nucleoside analogue. Claim 62 is drawn to pharmaceutical articles containing at least one nucleoside analogue and at least one compound capable of enhancing gap-junction communication as a combination for the simultaneous, separate or successive administration in cancer therapy.

Huang et al. teach that the administration of phenylbutyrate (an aromatic organic acid and a compound capable of enhancing gap-junction communication), which functions to enhance growth inhibition in fluorodeoxyuridine treated colon carcinoma cells. (See abstract) Therefore this disclosure of Huang et al. is interpreted as reading on the instant invention to the extent that it encompasses the administration of phenlybutyrate and the nucleoside analogue fluorodeoxyuridine.

Chung et al. (2000) teaches a method for treating nasopharyngeal carcinoma comprising administering phenylbutyrate and ganciclovir, see abstract.

Huang et al. and Chung et al. do not teach wherein the disclosed compositions are useful for the cancer therapy, wherein said cancer is a multicellular cancer type, or wherein the cancer is selected from the group consisting of glioblastoma, bladder cancer, neuroblastoma, esophageal cancer, tongue cancer, hepatocellular carcinoma, lung cancer, malignant melanoma, ovarian cancer, prostate cancer, renal cell carcinoma, and breast cancer. However, to the extent that the compositions of Huang et al. read on the pharmaceutical articles recited in the claims, absent evidence to the contrary, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 12, 21-31, 62-63, and 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over DiMartino in view of Yang et al. and Lavie et al.

8. DiMartino et al. (US6905669B2) teach compositions and methods are provided for treating diseases associated with aberrant silencing of gene expression such as

cancer by reestablishing the gene expression through inhibition of DNA hypomethylation and histone deacetylase. The method comprises: administering to a patient suffering from the disease a therapeutically effective amount of a DNA methylation inhibitor in combination with an effective amount of histone deacetylase inhibitor. In one aspect of this reference, the methods of DiMartino et al. are provided for treating chronic inflammatory disease comprising the administration of a composition comprising a DNA methylation inhibitor and a histone deacetylase inhibitor.

9. In one embodiment, the DNA methylation inhibitor is a cytidine analog or derivative. Examples of the cytidine analog or derivative include but art not limited to 5-azacytidine and 5-aza-2'-deoxycytidine. In a preferred variation of this embodiment, the DNA methylation inhibitor is 5-aza-2'-deoxycytidine (5-aza-CdR or decitabine).

10. According to this embodiment, the histone deacetylase inhibitor is selected from the group consisting of hydroxamic acids, cyclic peptides, benzamides, short-chain fatty acids, and depudecin. Examples of short-chain fatty acids include but are not limited to butyrates (e.g., butyric acid and phenylbutyrate (PB)).

11. DiMartino et al. also teach that the most prominent function of decitabine is its ability to specifically and potently inhibit DNA methylation. As described above for methylation of cytosine in CpG islands as an example, methylation of cytosine to 5-methylcytosine occurs at the level of DNA. Inside the cell, decitabine is first converted into its active form, the phosphorylated 5-aza-deoxycytidine, by deoxycytidine kinase which is primarily synthesized during the S phase of the cell cycle.

12. Murphy and DiMartino et al. do not teach the delivery of a deoxyribonucleoside kinase to a cell via expression from a stem cell.

13. Lavie et al. (US 20070258968A1) provides methods for enhancing efficiency of prodrugs by specifically engineered enzymes with enhanced activity towards nucleoside analogs used in cancer chemotherapy, and delivering the enzymes to specific target cells in a patient. The invention also provides modified deoxycytidine kinase (dCK) mutants with such enhanced activity.

14. Yang et al. (US 20060068481A1) describe nucleic acid sequences of human kinases for use in treating cancer. Yang et al. further teaches the following at ¶ [0222]: "[M]any methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. "

15. It would have been obvious to the ordinary skilled artisan at the time of the instant invention to modify the teachings of DiMartino et al. with the teachings of Lavie et al. and Yang et al. One of ordinary skill in the art would have been motivated to combine the teachings of the cited references in the design of the instant invention since the DiMartino et al. reference teaches compositions comprising deoxycytidine kinase, and Lavie et al. provides the nucleotide sequence of deoxycytidine kinase for exogenous expression of this gene. Moreover, Yang et al. teach that an alternative means for delivering kinases to the cells of a patient comprise the expression of the nucleic into stem cells taken from the patient and transplanting the autologous cells

back into the same patient. It would have been obvious to the ordinary skilled artisan at the time of the instant invention to substitute one alternative means of delivering exogenous nucleic acid into cells for another, with the expectation of producing similar results.

16. Claims 1, 12, 21-31, 62-63, and 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al. in view of Gold et al. and Jian et al.

17. Murphy et al. (US20020049151) teach compositions for the treatment of inflammatory immune diseases. In one embodiment, Murphy et al. teaches examples of suicide gene/prodrug combinations which may be used are Herpes Simplex Virus-thymidine kinase (HSVtk) and ganciclovir, acyclovir or FIAU; oxidoreductase and cycloheximide; cytosine deaminase and 5-fluorocytosine; thymidine kinase thymidylate kinase (Tdk::Tmk) and AZT; and deoxycytidine kinase and cytosine arabinoside. (See ¶ [0157]).

18. Gold et al. (US Patent No. 6576464) teach the expression of thymidine kinase from stem cells. Additionally, Gold et al. discloses the sequence of herpes simplex virus thymidine kinase gene (SEQ ID NO: 3 of US6576464). This sequence is 98.1% identical to SEQ ID NO: 3 of the instant application.

19. Jian et al. teach the combination of adenovirus mediated suicide gene therapy with the histone deacetylase inhibitors butyrate and phenylbutyrate, and the administration of this combination to bladder cancer *in vitro* and *in vivo*. Jian et al. teach that the use of butyrate or phenlybutyrate alone or in combination improves adenoviral

mediated suicide gene therapy. Jian et al. teach the combination of thymidine kinase gene expression with ganciclovir treatment.

20. It would have been obvious to the ordinary skilled artisan to modify the cited references at the time of the instant invention in the design of the instant invention. First, one of ordinary skill in the art would have been motivated to combine the suicide gene/prodrug compositions of Murphy et al. with the teachings of Jian et al., because Jian et al. teach that butyrate or phenlybutyrate alone or in combination improves adenoviral mediated suicide gene therapy. As per MPEP § 2144.06: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) .

21. Furthermore, it would have been obvious to substitute the thymidine kinase gene sequence of Murphy et al. with the sequence disclosed in Gold et al. One of ordinary skill in the art would have been motivated to make this substitution since it is obvious to substitute one art recognized equivalent thymidine kinase nucleotide sequence for another with the expectation of producing a composition having the same equivalent function. See MPEP 2144.06 [R-6]. "[A]n express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious."

Claim Rejections - 35 USC § 112

22. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claims 30-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

24. Regarding claim 31, the phrase "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

25. Regarding claim 30-31, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633